




Clinical science

# Association between corneal hysteresis and glaucoma in a Japanese population: the Hisayama Study

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## ABSTRACT

**Aims** To investigate the association between corneal hysteresis and the presence of glaucoma and its subtypes in a general Japanese population.

**Methods** We analysed the data of 2338 Japanese community-dwellers aged  $\geq 40$  years (1059 men, 1279 women) who underwent an eye examination in 2018 as part of the population-based, cross-sectional Hisayama Study. Participants were divided into quartile levels of corneal hysteresis, which had been measured with an ocular response analyzer. Glaucoma was defined based on the International Society of Geographical and Epidemiological Ophthalmology criteria. We conducted a logistic regression analysis to determine the ORs and their 95% CIs for the presence of outcomes according to the corneal hysteresis quartiles.

**Results** Glaucoma was diagnosed in 154 participants: primary open-angle glaucoma (POAG),  $n=115$ ; primary angle-closure glaucoma,  $n=17$ ; exfoliation glaucoma,  $n=21$  and secondary glaucoma without exfoliation glaucoma,  $n=1$ . After adjustment for confounders, the OR for prevalent glaucoma was significantly increased in the participants in the first corneal-hysteresis quartile compared with those in the fourth quartile (OR: 1.80; 95% CI: 1.03 to 3.17). Regarding glaucoma subtypes, the first-quartile participants had significantly greater likelihoods of the presence of POAG (OR: 1.63; 95% CI: 1.02 to 2.61) and exfoliation glaucoma (OR: 6.49; 95% CI: 1.44 to 29.30) compared with those in the third and fourth quartiles after adjustment for potential confounders.

**Conclusions** These results demonstrated a significant inverse association between corneal hysteresis and the likelihood of glaucoma, suggesting that the measurement of corneal hysteresis would provide useful information for elucidating the aetiology of glaucoma.

## INTRODUCTION

Glaucoma is the leading cause of blindness and vision loss worldwide, and it has a significant impact on an individual's quality of life.<sup>1,2</sup> Glaucoma has been diagnosed based on the evaluation of characteristic structural and functional abnormalities of the optic nerve, in accordance with the International Society of Geographical and Epidemiological Ophthalmology (ISGEO) criteria.<sup>3</sup>

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Only one population-based study has addressed the association between corneal hysteresis and glaucoma. It is worthwhile to clarify this association on the basis of the International Society of Geographical and Epidemiological Ophthalmology criteria in a general population.

## WHAT THIS STUDY ADDS

⇒ In this analysis of 2338 participants, lower corneal hysteresis was significantly associated with the presence of glaucoma in a general Japanese population. The likelihoods of the presence of primary open angle glaucoma and exfoliation glaucoma increased significantly with lower levels of corneal hysteresis.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings indicate that the measurement of corneal hysteresis would provide useful information for clarifying the aetiology of glaucoma.

The risk of the presence and the progression of glaucoma are influenced by corneal biomechanical characteristics.<sup>4,5</sup> The biomechanical properties of the cornea can be quantified as corneal hysteresis, which reflects the viscoelastic damping effect of corneal tissues, defined as the difference in air pulse pressure between inward and outward applanation forces.<sup>6</sup> Corneal hysteresis can be measured simultaneously with the intraocular pressure (IOP) with the use of non-contact tonometry with augmented functionality. Some hospital-based studies have shown that a lesser degree of corneal hysteresis is associated with higher risks of the presence and the progression of glaucoma.<sup>7-9</sup> Only one population-based study has addressed the association between corneal hysteresis and glaucoma, and the information on glaucoma was collected with a self-reported questionnaire.<sup>10</sup> It is thus worthwhile to clarify the association between corneal hysteresis and glaucoma diagnosed based on the ISGEO criteria by ophthalmologists in a general population.

The Hisayama Study is an ongoing, population-based epidemiological study of non-communicable diseases, including cardiovascular diseases and eye diseases, in a Japanese community.<sup>11</sup> We investigated the association between corneal hysteresis and glaucoma in approx. 2500 community-dwelling Japanese individuals enrolled in the Hisayama Study.

## MATERIALS AND METHODS

### Study population

The Hisayama Study is an ongoing, long-term observational study of cardiovascular disease and its risk factors in Hisayama,<sup>12 13</sup> a town adjacent to the metropolitan area of the city of Fukuoka in southwest Japan. As part of the Hisayama Study, a population-based epidemiologic ophthalmic survey of residents of Hisayama has been underway since 1998.<sup>14</sup> In 2018, a total of 2644 Hisayama residents aged  $\geq 40$  years underwent eye examinations. For the present study, we reviewed those individuals' data and excluded the data of seven participants who did not provide their consent for study participation and those of the 177 participants without available corneal hysteresis data, 49 participants with a waveform score  $< 5$  points, 8 participants who had undergone laser-assisted in situ keratomileusis, 63 participants with prostaglandin analogues and 2 participants with glaucoma surgery. A final total of 2338 participants (1059 men and 1279 women) were thus enrolled in the present study.

### Measurement of corneal hysteresis levels and other ophthalmic examinations

All of the ophthalmic examinations were performed by ophthalmologists trained in glaucoma diagnoses. The degree of corneal hysteresis was measured with an ocular response analyzer (ORA) (Reichert Corp, Carrollton, Texas, USA).<sup>6</sup> We divided the patients into four quartiles based on their levels of corneal hysteresis (Quartile 1:  $\leq 8.7$  mm Hg; Quartile 2: 8.8–9.5 mm Hg; Quartile 3: 9.6–10.2 mm Hg and Quartile 4:  $\geq 10.3$  mm Hg). The participants' IOP was measured three consecutive times with the same ORA.<sup>6</sup> Axial-length measurements were performed with non-contact partial coherence laser interferometry using an OA-2000 optical biometer (Tomey, Nagoya, Japan). The central corneal thickness (CCT) was measured using an anterior-segment CCT measurement apparatus (CASIA2; Tomey).

### Definition of glaucoma

The individuals with glaucoma were assigned to one of three categories according to the ISGEO criteria.<sup>3</sup> A glaucomatous visual field defect was identified based on the criteria proposed by Anderson and Patella.<sup>15</sup> The hemifield was judged to be abnormal when the pattern deviation probability plot showed a cluster of three or more non-edged contiguous points having sensitivity with a probability  $< 5\%$  in the upper or lower hemifield and in one of these with a probability  $< 1\%$ . The visual field test was repeated if the test reliability was not satisfactory (fixation loss,  $< 33\%$ ; false-positive and false-negative results,  $< 20\%$ ). A participant in a definitive examination was examined by gonioscopy. The same glaucoma fellowship-trained ophthalmologist (KF) performed all gonioscopy. Each gonioscopy was performed with a Goldmann two-mirror lens under standard dark illumination. A narrow, vertical, 1 mm beam was offset vertically for superior and inferior quadrants and horizontally for nasal and temporal quadrants.

The subtypes of glaucoma were defined according to the ISGEO criteria.<sup>3 16</sup> Exfoliation glaucoma was participants with glaucoma and exfoliation. Exfoliation was diagnosed based on

the findings obtained by slit-lamp biomicroscopy if there was whitish exfoliation material along the pupillary margin and/or the anterior lens capsule. Participants were classified as having exfoliation if any exfoliation material was present in either eye.

An occludable angle was defined as an angle in which the posterior trabecular meshwork was not visible during static gonioscopy in at least three-quarters of the angle circumference in the primary position without manipulation or indentation.<sup>3 17</sup> In the individuals who had undergone cataract surgery, both the findings of the operated eye (laser iridotomy, exfoliation, history of glaucoma surgery) and the findings of the fellow eye were considered as much as possible to rule out other subtypes of glaucoma.<sup>18</sup>

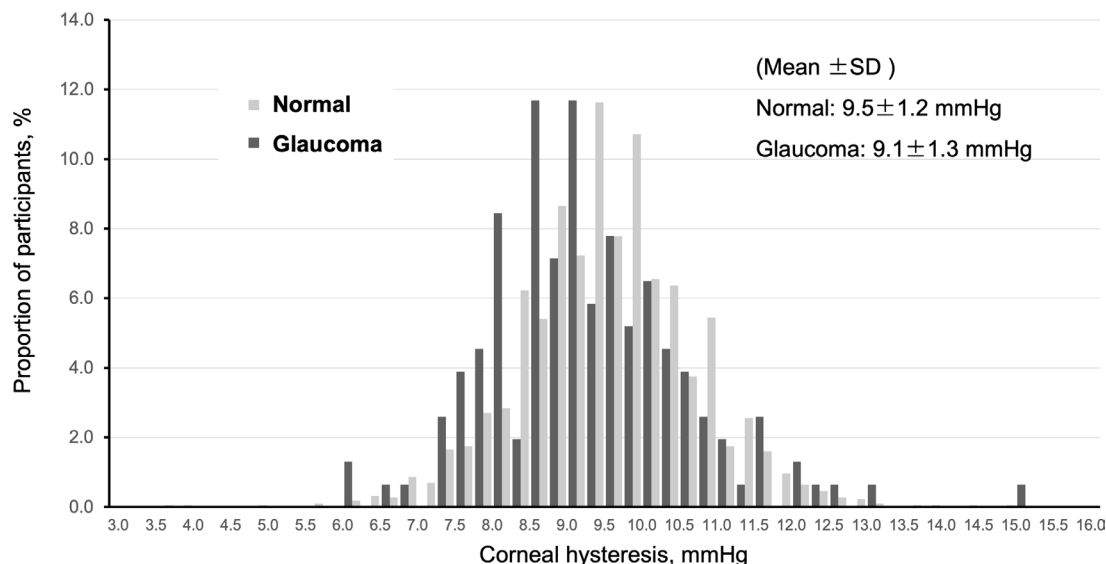
### Clinical evaluation and laboratory measurements

The clinical evaluation and laboratory measurements were performed in the screening examination. Each individual's blood pressure was measured three times by an automated sphygmomanometer after he or she had rested for  $\geq 5$  min in a sitting position. The average of the three measurements was used for the analysis. Hypertension was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg or the current use of antihypertensive medication. Blood samples were collected from an antecubital vein after a  $\geq 12$ -hour overnight fast. Plasma glucose levels were measured by the hexokinase method. Diabetes was defined as a fasting plasma glucose level  $\geq 7.0$  mmol/L, a 2-hour 75 g oral glucose post-load or casual glucose level  $\geq 11.1$  mmol/L or the current use of any antidiabetic medication (oral hypoglycaemic agent, injectable glucagon-like peptide analogue or insulin). Serum total cholesterol levels were determined enzymatically.

The participant's body height and weight were measured in light clothing without shoes, and the body mass index ( $\text{kg}/\text{m}^2$ ) was calculated. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation with a coefficient of 0.813 for Japanese individuals.<sup>19</sup> Information on the participant's exercise during leisure time, smoking habits and alcohol intake was obtained using a standard questionnaire. The questionnaire was administered to each individual and was checked by trained interviewers at the screening. Smoking habits and alcohol intake were classified as current habitual use or no current habitual use. Patients engaging in sports  $\geq 3$  times/week during their leisure time were defined as the regular exercise group.

### Statistical analysis

The SAS software package (V.9.4; SAS, Cary, North Carolina, USA) was used to perform all statistical analyses. The ophthalmic data from the right eye were basically used for individuals, but the ophthalmic data from the left eye were used when the data from the right eye was not available or when only the left eye had glaucoma. Age-adjusted and sex-adjusted mean values or frequencies of risk factors across the corneal hysteresis quartiles were estimated and tested by a linear or logistic regression analysis, respectively. The age-adjusted and sex-adjusted or multivariable-adjusted ORs and their 95% CIs of corneal hysteresis for the presence of glaucoma were estimated by a logistic regression analysis. In the multivariable-adjusted model, the known and plausible risk factors for glaucoma (ie, age, sex, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, current smoking, current alcohol drinking, regular exercise, IOP, axial length and CCT) were included as covariates. We also applied the variable



**Figure 1** Distribution of corneal hysteresis.

selection analysis method using backward variable selection, in which the variables for which the probability (p) value was <0.20 were used in the relevant model. Age was included in every model, and the other covariates were selected with a backward elimination procedure. A two-tailed p value <0.05 was considered significant in all analyses.

**RESULTS**

**Figure 1** depicts the distributions of corneal hysteresis. The mean (SD) of corneal hysteresis was 9.5 (1.2) mm Hg among all 2338 participants; 9.5 (1.2) mm Hg among the participants without glaucoma (n=2184; 93.4%) and 9.1 (1.3) mm Hg among those with glaucoma (n=154; 6.7%). The mean of corneal hysteresis in the glaucoma group was significantly higher than in the normal group (p<0.001).

With regard to the subtypes of glaucoma, 115 participants (4.9% of the total participants) presented with primary open angle glaucoma (POAG), 17 participants (0.7%) with primary angle-closure glaucoma (PACG), 21 participants (0.9%) with exfoliation glaucoma and 1 participant (0.04%) with secondary glaucoma without exfoliation glaucoma.

The age-adjusted and sex-adjusted baseline characteristics of the study population according to each quartile of corneal hysteresis are shown in **table 1**. The mean IOP, CCT and the proportions of the participants with diabetes, smoking habits and current alcohol drinking increased significantly with higher levels of corneal hysteresis (all P for trend <0.05). The mean age, axial length and the proportion of men decreased significantly with higher levels of corneal hysteresis (all P for trend <0.05).

**Table 2** provides the age-adjusted and sex-adjusted and multivariable-adjusted ORs for the presence of glaucoma according to the quartiles of corneal hysteresis. In the age-adjusted and sex-adjusted model, the ORs of prevalent glaucoma were significantly increased in the participants in the lowest quartile of corneal hysteresis (Quartile 1) compared with those in the highest quartile (Quartile 4) (OR: 1.91; 95% CI: 1.16 to 3.16; p=0.01). This association was essentially unchanged after adjustment for age, sex, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, current smoking, current alcohol drinking, regular exercise,

IOP, axial length, CCT and use of IOP-lowering medications (OR: 1.80; 95% CI: 1.03 to 3.17; p=0.04), and it was also essentially unchanged in the variable selection analysis method (OR: 1.94; 95% CI: 1.15 to 3.27; p=0.01).

We also examined the association between corneal hysteresis and the subtypes of glaucoma (**table 3**). Among the 154

**Table 1** Age-adjusted and sex-adjusted baseline characteristics of participants according to the quartiles of cornea hysteresis

Variable	Cornea hysteresis levels, mm Hg				P for trend
	Quartile 1 (≤8.7)	Quartile 2 (8.8–9.5)	Quartile 3 (9.6–10.2)	Quartile 4 (≥10.3)	
	n=571	n=640	n=572	n=555	
Age, years	69.7 (0.5)	65.0 (0.5)	62.7 (0.5)	60.8 (0.5)	<0.001
Men, %	53.0	45.7	43.7	38.6	<0.001
Hypertension, %	49.7	44.9	49.1	50.9	0.43
Diabetes, %	14.3	13.1	17.2	18.4	0.02
Serum total cholesterol, mmol/L	5.40 (0.05)	5.33 (0.04)	5.33 (0.04)	5.29 (0.04)	0.07
Body mass index, kg/m <sup>2</sup>	23.2 (0.2)	23.3 (0.1)	23.3 (0.1)	23.3 (0.2)	0.92
eGFR, mL/min/1.73 m <sup>2</sup>	69.6 (0.4)	69.8 (0.4)	69.2 (0.4)	69.5 (0.4)	0.63
Current smoking, %	7.0	10.8	11.3	16.4	<0.001
Current alcohol drinking, %	49.9	53.3	53.7	57.4	0.03
Regular exercise, %	16.2	17.1	17.7	12.5	0.15
IOP, mm Hg	12.9 (0.1)	13.1 (0.1)	13.5 (0.1)	14.1 (0.1)	<0.001
Axial length, mm	23.9 (0.1)	23.8 (0.1)	23.7 (0.1)	23.7 (0.1)	0.03
Central corneal thickness, μm	513 (1)	526 (1)	535 (1)	550 (1)	<0.001
IOP-lowering medication, %	1.4	0.6	0.5	0.8	0.26

Values are means (SE) or %.  
eGFR, estimated glomerular filtration rate; IOP, intraocular pressure.

**Table 2** OR for glaucoma according to the quartiles of corneal hysteresis

Corneal hysteresis, mm Hg	No. of cases/participant	Age-adjusted and sex-adjusted		Multivariable-adjusted*		Multivariable-adjusted†	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Quartile 1 (≤8.7)	66/571	1.91 (1.16 to 3.16)	0.01	1.80 (1.03 to 3.17)	0.04	1.94 (1.15 to 3.27)	0.01
Quartile 2 (8.8–9.5)	39/640	1.17 (0.69 to 1.99)	0.55	1.22 (0.70 to 2.16)	0.47	1.28 (0.74 to 2.21)	0.38
Quartile 3 (9.6–10.2)	25/572	0.91 (0.51 to 1.63)	0.77	0.97 (0.53 to 1.77)	0.92	0.99 (0.54 to 1.79)	0.96
Quartile 4 (≥10.3)	24/555	1.00 (ref.)		1.00 (ref.)		1.00 (ref.)	
P for trend		0.002		0.02		0.005	

\*Multivariable adjustment made for age, sex, hypertension, diabetes, serum total cholesterol, body mass index, estimated glomerular filtration rate, current smoking, current alcohol drinking, regular exercise, IOP, axial length, central corneal thickness and IOP-lowering medications  
 †The multivariable regression analysis was performed with a backward selection procedure. Multivariable adjustments were made for age, estimated glomerular filtration rate, axial length and IOP-lowering medications.  
 IOP, intraocular pressure.

participants with glaucoma, 115 had POAG, 17 had PACG and 21 had exfoliation glaucoma. In this analysis, the participants in the third and fourth quartiles of corneal hysteresis were combined as a reference group due to the small number of participants with PACG and exfoliation glaucoma. The results of the variable selection analysis method revealed that the participants in the first quartile were significantly more likely to have POAG compared with the reference group (OR: 1.63; 95% CI: 1.02 to 2.61; p=0.04). After the adjustment for age and IOP-lowering medication use, the participants in the first corneal-hysteresis quartiles were significantly more likely to have exfoliation glaucoma than those in the reference group (OR: 6.49; 95% CI: 1.44 to 29.30; p=0.02). The OR of the presence of PACG in

the lowest quartile of corneal hysteresis was somewhat high but did not reach significance (OR: 1.37; 95% CI: 0.42 to 4.46; p=0.60). The association between corneal hysteresis and secondary glaucoma without exfoliation glaucoma could not be assessed due to the small number of participants with secondary glaucoma without exfoliation glaucoma (n=1).

**DISCUSSION**

The results of our analyses of 2338 Japanese community-dwellers aged ≥40 years demonstrated that after adjustment for potential confounding factors, a lower level of corneal hysteresis as estimated by an ORA was significantly associated with a greater likelihood of glaucoma. We also observed that the likelihoods of the presence of POAG and exfoliation glaucoma increased significantly with lower levels of corneal hysteresis. Moreover, the ORs for a lower degree of corneal hysteresis and for exfoliation glaucoma were higher than the ORs for POAG, suggesting that the association between corneal hysteresis and exfoliation glaucoma may be stronger than POAG. These findings may provide contribute to the clarification of the aetiology of glaucoma.

In some hospital-based cross-sectional studies, participants with glaucoma were observed to have less corneal hysteresis than those without glaucoma.<sup>8,9</sup> A hospital-based longitudinal study reported that in patients with glaucoma, a lower degree of corneal hysteresis was significantly associated with a greater progression of glaucoma over a 4-year period.<sup>20</sup> A single population-based investigation, the UK Biobank study, revealed that the OR for the presence of glaucoma increased significantly with lower corneal hysteresis in participants with glaucoma, but the participants' glaucoma information was collected by a self-reported questionnaire.<sup>10</sup> Our findings are consistent with the results of these reports. The present study also revealed a significant association between lower corneal hysteresis and a greater risk of the presence of glaucoma and its subtypes on the basis of more reliable information, that is, diagnoses by ophthalmologists using the ISGEO criteria in a general population.

The exact mechanisms underlying the association between corneal hysteresis and the likelihood of the presence of glaucoma are unclear, but some mechanisms can be considered. First, corneal hysteresis may be an indicator that could be used to determine the structural susceptibility of the lamina cribrosa related to the glaucomatous change of the optic nerve. Histological examinations demonstrated that lamina cribrosa displacement played an important role in the aetiology of glaucoma,<sup>21,22</sup> and a clinical study by Lanzagorta-Aresti *et al* revealed a significant association between lower corneal hysteresis and decreased displacement of the lamina cribrosa.<sup>23</sup> Second, lower corneal hysteresis may reflect a stiffening of the peripapillary sclera

**Table 3** ORs for subtypes of glaucoma according to the quartiles of corneal hysteresis

Corneal hysteresis, mm Hg	No. of cases/participants	Multivariable-adjusted*	
		OR (95% CI)	P value
<b>POAG<sup>†</sup></b>			
Quartile 1 (≤8.7)	45/571	1.63 (1.02 to 2.61)	0.04
Quartile 2 (8.8–9.5)	29/640	1.17 (0.71 to 1.92)	0.55
Quartiles 3 and 4 (≥9.6)	41/1127	1.00 (ref.)	
P for trend		0.04	
<b>PACG<sup>‡</sup></b>			
Quartile 1 (≤8.7)	6/571	1.37 (0.42 to 4.46)	0.60
Quartile 2 (8.8–9.5)	5/640	1.27 (0.38 to 4.21)	0.70
Quartiles 3 and 4 (≥9.6)	6/1127	1.00 (ref.)	
P for trend		0.60	
<b>Exfoliation glaucoma<sup>§</sup></b>			
Quartile 1 (≤8.7)	14/571	6.49 (1.44 to 29.30)	0.02
Quartile 2 (8.8–9.5)	5/640	3.40 (0.65 to 17.82)	0.15
Quartiles 3 and 4 (≥9.6)	2/1127	1.00 (ref.)	
P for trend		0.01	

\*The multivariable regression analysis was performed with a backward selection procedure.  
 †Multivariable adjustments were made for age, estimated glomerular filtration rate, current alcohol drinking, axial length and IOP-lowering medications.  
 ‡Multivariable adjustments were made for age and sex.  
 §Multivariable adjustments were made for age and IOP-lowering medications.  
 IOP, intraocular pressure; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma .



(which involves lower resistance to mechanical damage), because the extracellular matrix in the cornea and that in the sclera have a common structure.<sup>24–27</sup> Evidence obtained with experimental models suggested that a stiffer sclera may be less prone to optic nerve damage.<sup>28–29</sup> Taken together, the present and previous findings indicate that corneal hysteresis reflects structural weakness and stiffness against the stress of posterior ocular tissues surrounding the optic nerve head, which may lead to the pathogenesis of glaucoma.

The present participants' CCT was measured as a structural characteristics of the cornea. It was reported that a thinner CCT was independently associated with the presence and incidence of glaucoma.<sup>4–5</sup> Our present analyses revealed a significant association between the CCT and corneal hysteresis (Pearson's  $r=0.40$ ,  $p<0.001$ ). In the multivariable analysis, even with the adjustment for CCT, corneal hysteresis remained an independent factor associated with glaucoma. This may indicate that one or more mechanisms other than a mechanism involving the CCT contribute to the association between corneal hysteresis and glaucoma.

The strengths of the present study were the population-based design, the accurate determination of glaucoma based on the ISGEO criteria and the detailed evaluation of confounding factors. Nevertheless, there are potential limitations to address. Because this was a cross-sectional study, a conclusion about a causal relationship between corneal hysteresis and glaucoma could not be made. Second, we did not observe a significant association between corneal hysteresis and the presence of PACG, probably because of the small number of participants. PACG has been acknowledged to be strongly associated with visual impairment. Further large-scale studies are necessary to elucidate this issue. Third, there is a possibility of selection bias due to the exclusion of participants from this study because of a lack of information in some cases; 299 individuals were excluded from the analyses due to a lack of information. We thus compared characteristics between the 2338 individuals who were included in the analysis and the 299 excluded individuals, and the results are available in online supplemental table S1. The excluded individuals were younger, more likely to be women, and more likely to have lower mean serum total cholesterol and body mass index, and higher mean estimated glomerular filtration rate, IOP, axial length and CCT values, and higher frequencies of the use of IOP-lowering medications compared with the included individuals. The excluded population is thus likely to have been a healthier population. Finally, the generalisability of our findings may be limited because the study was conducted in only one community in Japan.

In conclusion, the results of this cross-sectional study revealed that in a general Japanese population, a lower degree of corneal hysteresis was significantly associated with a higher likelihood of glaucoma. Further prospective studies are required to evaluate the causal association between corneal hysteresis and the development of glaucoma.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

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